

**REMARKS**

Claims 1-185 are pending in the present application. Claims 16-31, 56-81, 97-112, 137-162, 166, 167 and 172-185 have been withdrawn from consideration.<sup>1</sup> Claims 1-15, 32-55, 82-96, 113-136, 163-165 and 168-171 are rejected. By virtue of this response claims 4, 5, 35, 85, 86 and 116 have been cancelled, and claims 1, 13, 32, 36, 44, 82, 94, 113, 117, 125, 168, 170, and 171 have been amended. Accordingly, claims 1-3, 6-15, 32-34, 36-55, 82-84, 87-96, 113-115, 117-136, 163-165, and 168-171 are currently under consideration. No new matter is added by this amendment. Support for the amended and new claims is found in the originally filed claims and the specification, as further discussed below. *See, e.g.* page 52, lines 12-13; Example 2 (pages 127-128; *see also* page 125, line 37).

With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Applicant respectfully brings to the Office's attention the following pending U.S. patent applications that are owned by the assignee of the present application: U.S. Serial Nos. 09/893,191; 09/990,531; 09/974,756; 10/017,880; 10/100,321; 10/096,221; 10/386,622; 10/404,895; and 10/441,663. Applicant also directs the Office's attention to issued U.S. Patent No. 6,251,639, which is owned by the assignee of the present application.

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<sup>1</sup> Applicant notes that the Office Action Summary lists claims 1-15, 32-55, 82-96, 113-136, 163-165, and 168-171 as allowed. At the interview, the Examiner confirmed that this was an error, and that these claims are withdrawn, not allowed.

***Interview***

Applicant thanks Examiner Spiegler for extending the courtesy of the helpful telephonic interview with Applicant's representative held August 4, 2003, with Primary Examiner Horlick. This response reflects the results of that interview.

***Information Disclosure Statement***

During the interview, the Examiner stated that he did not have copies of any of the references submitted with the Information Disclosure Statement submitted on February 20, 2002, but that he did have copies of the Form 1449 submitted with that filing. The Examiner requested resubmission of scientific papers submitted in that IDS, but indicated that it was not necessary to resubmit copies of patents and patent publications filed with that IDS. Applicant will prepare the copies and submit them shortly under separate cover. In addition, Applicant notes that a Supplemental IDS is being prepared and will be submitted shortly. Applicant would appreciate if the Examiner could initial the Form PTO-1449s to indicate that he reviewed the references and return a copy of the initialed 1449s to Applicant.

***Rejections under 35 U.S.C. § 112, second paragraph***

Claims 1-15, 32-55, 82-96, 113-136, 163-165 and 168-171 are rejected under 35 USC 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Several grounds for rejection are provided in the Office Action. Applicant will discuss these in turn.

As a preliminary matter, Applicant notes that the test for definiteness under 35 U.S.C. §112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). The "Advance notice of changes to

MPEP § 2173.02"<sup>2</sup> states if the claim language selected by applicants satisfies the statutory requirements of 35 U.S.C. § 112, second paragraph, but the examiner merely wants the applicant to improve the clarity or precision of the language used, the claim must not be rejected under 35 U.S.C. § 112, second paragraph.

(A) Claims 1-15, 32-55, 82-96, 113-136, 163-165, and 168-171

Claims 1-15, 32-55, 82-96, 113-136, 163-165, and 168-171 are rejected as allegedly indefinite for reciting the term "about". Applicant respectfully traverses this rejection.

As discussed during the interview, the use of the term "about" does not render claims using this term indefinite. It is well established that the use of a relative term does not render a claim indefinite under 35 USC § 112, second paragraph. *See Seattle Box Co. v. Industrial Crating & Packaging, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984) (stating that the fact that the claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite); *see also Manual of Patent Examining Procedure* § 2173.05(b). Moreover, the term "about" is accepted and widely used in patent practice and is clearly acceptable under the law. "About" is neither broad nor arbitrary, but rather serves as a flexible term with a meaning similar to "approximately." *See Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217-18 (Fed. Cir. 1995); *Conopco, Inc. v. May Dep't Stores Co.*, 46 F.3d 1556, 1561 (Fed. Cir. 1994); *Ex parte Eastwood*, 163 USPQ 316 (Brd. App. 1968); *see also U.S. Patent & Trademark Office, Manual of Patent Examining Procedure* § 2173.05(b). Accordingly, Applicant respectfully submits that the use of the term "about" is proper under the caselaw, the MPEP and under USPTO policy.

However, to expedite prosecution, claims 1, 32, 82, 96, 113, 163, and 168 have been amended to clarify and increase the precision of the claims, and now recite that "the 3' most nucleotide of the DNA portion of the composite primer hybridizes from 1 to about 10 nucleotides from the sequence of interest", as suggested by the Examiners. Support for this amendment is found

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<sup>2</sup> "Advance notice of changes to MPEP § 2173.02 clarifying Office policy with respect to rejections made under 35 U.S.C. § 112, second paragraph in view of the Supreme Court holding in *Festo Corp. v. ...*" Memorandum from Stephen Kunn to the Patent Examining Corp. dated January 17, 2003).

in the specification at, e.g., page 52, lines 12-13; Example 2 (pages 127-128; *see also* page 125, line 37); *see also* originally-filed claims 1, 32, 82, 113, 163, and 168. At the interview, the Examiners stated that this amendment would obviate this rejection. Accordingly, withdrawal of this rejection is respectfully requested.

(B) Claims 1-15 and 32-55

Claims 1-15 and 32-55 are rejected as allegedly indefinite for reciting "essentially the same conditions as those for primer extension". Applicant respectfully traverses this rejection.

As discussed during the interview, the use of the term "essentially" does not render these claims indefinite. As noted above, it is well established that the use of a relative term does not render a claim indefinite under 35 USC § 112, second paragraph. The term "essentially" is accepted and widely used in patent practice and is clearly acceptable under the law. *See, e.g., Manual of Patent Examining Procedure* § 2173.05(b); *In re Masoni*, 218 USPQ 289 (CCPA 1983) (use of the term "essentially" in a claim held definite). Moreover, those skilled in the art would understand what is claimed when the claim is read in light of the specification, which defines "essentially the same conditions" and "conditions that permit primer extension" as follows:

"Essentially the same conditions," as used herein, refer to conditions that are similar, but not necessarily identical (although the term does include identical conditions), in their chemical, physical, and or physicochemical properties and characteristics. Conditions are essentially the same if variances between the conditions in question are within variance ranges that one of skill in the art would not expect to substantially alter the primary function or effect of the conditions with respect to the reactions for which the conditions are used. The reactions for which the conditions are used include primer extension (polymerization), oligonucleotide attachment (such as ligation by DNA ligase), primer or oligonucleotide hybridization, and dissociation of cleaved primer extension and attached oligonucleotide combination products (Specification, page 46, lines 10-20);

and

conditions that "permit" primer extension are conditions that are conducive to polymerization of deoxyribonucleotide triphosphates

(dNTPs) and or analogs thereof from a primer that is hybridized to a target polynucleotide" (Specification, page 46, lines 25-29).

Accordingly, Applicant respectfully submits that the scope of the phrase "essentially the same conditions as those for primer extension" is clear. Withdrawal of this rejection is respectfully requested. At the interview, the Examiners indicated that this rejection would likely be withdrawn.

(C) Claims 13-14, 44-45, 94-95, and 125-126

Claims 13-14, 44-45, 94-95, and 125-126 are rejected as allegedly indefinite on the ground that "it is not clear that these claims further limit claim 1, 32, 82, 113, respectively". Applicant respectfully traverses this rejection.

As discussed at the interview, Applicant notes that the alleged failure to further limit the subject matter of a previous claim is not a proper basis for a rejection under § 112, second paragraph. Rather, as stated in the MPEP, claims that are in improper dependent form for failing to further limit the subject matter of a previous claims should be objected to under 37 CFR § 1.75(c). *See* MPEP § 608.01(n) (page 600-76). Accordingly, Applicant submits that the rejection of this claim under § 112, second paragraph, is improper. Withdrawal of this rejection is respectfully requested.

Applicant submits that these claims do further limit the independent claims from which they depend. However, to expedite prosecution and to increase the clarity and precision of the claims, claims 13, 44, 94, and 125 are amended to recite that the "target polynucleotide is generated by amplification". Applicant submits that this amendment clarifies that the target polynucleotide can be generated by an amplification, and further that generation of the target polynucleotide is distinct from generating multiple copies of the sequence of interest from the template polynucleotide. This amendment is implicit in the claims as previously pending, and is a non-narrowing, cosmetic amendment. Withdrawal of this rejection is respectfully requested.

***Obviousness-type double Patenting***

Claims 1-15, 32-55, 82-96, 113-136, 163-165, 168-171 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-116 of U.S. Patent No. 6,251,639 (" '639 patent"), in view of Soderlund et al. (USPN 6,013,431) ("Soderland"). The Office Action quotes the text of claims 1 and 2 of the '639 patent, and further references claim 23 and 27 of the '639 application. The Office Action also states:

the claims of the '639 [patent] differ from the claims of the instant application in that does[sic] not disclose the limitation that the 3' most DNA portion of the primer hybridizes from about 1 to about 10 nucleotides from the sequence of interest. However, hybridizing a primer near a sequence of interest is well known in the art to aid in identifying variations. For example, Soderland et al. teaches the hybridization of the 3' most nucleotide of the 3' DNA portion of a primer for identifying single nucleotide variations (see Figs. 1-3, cols. 3-9). *See* Office Action, pages 4-5.

Applicant respectfully traverses this rejection. A double patenting rejection relies on a comparison of the claims of the application at issue with the claims in the patent over which the application claims are rejected. *See* MPEP § 804. When the application at issue is a later-filed application, as in the present rejection, a one-way analysis of obviousness is needed, i.e., whether the invention defined in a claim in the application is an obvious variation of the invention defined in a claim in the patent. *See id.*; *see also In re Berg*, 46 USPQ2d 1226 (Fed. Cir. 1998). The analysis employed in an obviousness-type double patenting rejection parallels the guidelines or analysis of a 35 U.S.C. § 103 obviousness determination. *See* MPEP § 804.

Applicant respectfully submits that claims 1-15, 32-55, 82-96, 113-136, 163-165, 168-171 are patentably distinct over claims 1-116 of the '639 patent.

The Examiner states that "the claims of the '639 [patent] differ from the claims of the instant application in that does not disclose the limitation that the 3' most DNA portion of the primer hybridizes from about 1 to about 10 nucleotides from the sequence of interest". As discussed during

the interview. Applicant respectfully submits that the claims of the '639 patent differ in several additional respects from the claims of the present application. Claim 1 of the '639 patent recites:

1. A method for amplifying a polynucleotide sequence complementary to a target polynucleotide sequence comprising:
  - (a) hybridizing a single stranded DNA template comprising the target sequence with a composite primer, said composite primer comprising an RNA portion and a 3' DNA portion;
  - (b) optionally hybridizing a polynucleotide comprising a termination polynucleotide sequence to a region of the template which is 5' with respect to hybridization of the composite primer to the template;
  - (c) extending the composite primer with DNA polymerase;
  - (d) cleaving the RNA portion of the annealed composite primer with an enzyme that cleaves RNA from an RNA/DNA hybrid such that another composite primer hybridizes to the template and repeats primer extension by strand displacement,whereby multiple copies of the complementary sequence of the target sequence are produced.

Applicant directs the Office's attention to clause (d) of claim 1, above, which recites "cleaving the RNA portion of the annealed composite primer with an enzyme that cleaves RNA from an RNA DNA hybrid such that another composite primer hybridizes to the template and repeats primer extension by strand displacement".

By contrast, claim 1 of the instant application recites (in part) "cleaving the RNA portion of the primer extension product of (b) with an enzyme that cleaves RNA from an RNA DNA hybrid such that the cleaved primer extension product dissociates from the target polynucleotide, wherein the primer extension product is of a size that when the RNA is cleaved the cleaved primer extension product dissociates<sup>3</sup> from the target polynucleotide under essentially the same conditions as those

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<sup>3</sup> The specification of the present application defines the word "dissociation" as follows: "Dissociation" of a product from a polynucleotide, as used herein, refers to dissociation of a product (generally cleaved primer extension or cleaved attached oligonucleotide combination product) from a target polynucleotide due to decreased affinity of hybridization to the target polynucleotide following cleavage of the cleavable component of the product. Specification, page 48, lines 6-10.

for primer extension"; and claim 1 *does not* include the limitation that "another composite primer hybridizes to the template and repeats primer extension by strand displacement."

Accordingly, it is evident that claim 1 of the present application differs from claim 1 of the '639 patent in at least three aspects in addition to the difference noted in the Office Action (i.e., that the '639 patent "does not disclose the limitation that the 3' most DNA portion of the primer hybridizes from about 1 to about 10 nucleotides from the sequence of interest").

In the Office Action, however, the Examiner did not demonstrate that the claims of the '639 patent teach or suggest generation of primer extension product of a size that when the RNA is cleaved the cleaved primer extension product dissociates from the target polynucleotide, and dissociation of the cleaved primer extension product, as that phrase is used in the present application. And the Examiner did not show a suggestion or motivation to modify the teaching of the claims of the '639 patent, such that the requirement that "another composite primer hybridizes to the template and repeats primer extension by strand displacement" is deleted or modified. The Soderland patent does not remedy this deficit. Accordingly, Applicant respectfully submits that the pending claims are patentably distinct with respect to claims 1-116 of the '639 patent. Withdrawal of this rejection is respectfully requested.

With respect to claims 2, 23 and 27 of the '639 patent, which are also noted in the Office Action, Applicant points out that claim 2 is similar to claim 1, but recites the additional requirement of "(e) hybridizing a polynucleotide comprising a propromoter and a region which hybridizes to the displaced primer extension product under conditions which allow transcription to occur by RNA polymerase, such that RNA transcripts are produced comprising sequences complementary to the displaced primer extension products, whereby multiple copies of the target sequence are produced." Claim 23 requires amplification by the method of claim 1 or 2, and recite the additional steps of:

- (ii) comparing the amplification products if any from step (i) with the amount of amplification products from a reference template wherein
- (1) production of detectably fewer amplification products from the template as compared to the amount of amplification products from the reference template which comprises a region complementary to the

RNA portion of the composite primer indicates that the target polynucleotide does not comprise a sequence complementary to the RNA portion of the composite primer and is a sequence variant with respect to the sequence complementary to the RNA portion of the composite primer; or (2) production of detectably more amplification products from the template as compared to the amount of amplification products from the reference template which does not comprise a region which is complementary to the RNA portion of the composite primer indicates that the target polynucleotide comprises a sequence complementary to the RNA portion of the composite primer and is not a sequence variant with respect to the sequence complementary to the RNA portion of the composite primer.

Claim 27 requires amplification by the method of claim 1 or 2, and recites the additional step of "analyzing the amplification products for single stranded conformation . . . ." Accordingly, it is evident that claims 2, 23, and 27 each depend from claim 1 and/or recite additional limitations not discussed in the Office Action. Thus, these claims are also patentably distinct from the pending claims, and the obviousness-type double patenting rejection may be properly withdrawn.

Similarly, the remaining claims of the '639 patent depend from claim 1 or 2, and/or recite additional limitations that are not disclosed in the claims of the present application. Claims 31-63, and 115-116 are kit, composition or reaction mixture claims, all of which require a termination polynucleotide. The claims of the present application do not recite this component. Independent claims 19 and 20 are to methods of sequencing, and recite additional steps not recited in the methods of the present application. Independent methods claims 23, 27, 30, 79, 92 and 108 recite amplification by the method of claim 1 and/or 2, and/or recite additional limitations that are not disclosed in the claims of the present application (e.g., attachment to a surface; analysis by SSCP). Accordingly, it is evident that these claims each depend from claim 1 or 2 and/or recite additional limitations not discussed in the Office Action. Thus, these claims are also patentably distinct from the pending claims, and the obviousness-type double patenting rejection may be properly withdrawn.

For the above-stated reasons, withdrawal of this rejection is respectfully requested.

**CONCLUSION**

Applicant has, by way of the amendments and remarks presented herein, made a sincere effort to overcome rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 492692000300.

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